
Towards Improved Force Fields: III. Polarization through Modified Atomic Charges

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ABSTRACT: A method of modeling polarization by representing an atomic-centered induced dipole as a set of induced charges on the atom and its immediate neighbors is presented. The method is based on earlier work on deriving atomic charges from a distributed multipole analysis (P. J. Winn et al., *J Phys Chem A* 1997, 101, 5437; G. G. Ferenczy, *J Comput Chem* 1991, 12, 913). The method has been applied to the water dimer, water trimers, formaldehyde–water complexes, methanol complexes, and DNA basepairs. It was found that the induced charges described the various cooperative and anticooperative hydrogen bonding systems well, both qualitatively and quantitatively (as compared with Hartree–Fock calculations). Importantly, it has been shown that, when an induced charge (or induced dipole) model is used for larger molecules, a correction term is required for the underlying electrostatics. © 1999 John Wiley & Sons, Inc. *J Comput Chem* 20: 704–712, 1999

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Introduction

Polarization effects are extremely important in intermolecular interactions as they contribute a significant proportion of the interaction energy.¹ In some systems, polarization of the wavefunction and of its associated charge density may be an essential prerequisite for reaction. Consequently, there has been much interest in modeling polarization effects. In the present study, we implement an induced charge model to treat induction effects. Here we use the term *induction* to describe the deformation of the charge density in the electrostatic field of the environment. We use the term *polarization* in a broader sense to describe all effects causing the deformation of the charge density associated with the isolated molecule. Thus, polarization involves induction and also changes in charge density resulting from conformational changes. The usual approach for the treatment of induction effects involves the use of induced dipoles,² but there are a number of disadvantages with this approach. First, it is difficult to interpret induced dipoles to obtain chemical understanding. Second, it is inconsistent in that the primary electrostatic effects are usually modeled using lower rank atomic charges, whereas the less important polarization effects are handled using higher rank atomic dipoles. Third, and most importantly, it is computationally expensive.³ Some progress has been made to reduce this latter problem,⁴ but the other problems remain. The method implemented here has been useful for investigating induction effects in hydrogen bonded networks. It has also been particularly useful in highlighting a potential problem in the contamination of electrostatic potential fitted charges by internal induction effects.

There have been a number of approaches to modeling polarization effects by modifying the atomic charges. Rappe and Goddard have approached this by requiring that the electrostatic component of the chemical potential remains constant.⁵ Sprik has used the induced dipole as a constraint to be reproduced by treating the atomic charges as variables in a molecular dynamics simulation.⁶ Although both of these approaches are appealing, particularly when combined, as in the work of Rick and Berne,⁷ there are advantages in approaches in which the underlying atomic charges are defined precisely; for example, in potential

derived charges.⁸ Zhu has shown that for small, regular-shaped molecules, it is possible to define the induced dipole by a set of atomic charges.⁹ In some ways, our method is an elegant generalization of this approach, but the methodology is quite different and there are many additional benefits.

In previous articles we have shown how the potential from a wave function expressed as a distributed multipole analysis¹⁰ may be reproduced either by a set of atomic charges^{1,11,12} or by a set of effective multipoles.¹³ (These atomic charges have many advantages over standard potential derived charges,¹ as do the effective dipoles that closely mimic the effects of a DMA up to quadrupole or even octopole.¹³) It is therefore reasonably straightforward to reproduce an atom-centered induced dipole by a set of atomic charges, q' , on the atom and its neighbors. There are considerable advantages in doing this through a framework that may be consistently applied to model not only the electrostatics, but also polarization—either at the atomic charge level as described here or at the atomic dipole level.¹³ Moreover, unlike other methods that are most naturally applicable to molecular dynamics simulations,⁶ this approach may also find applications in hybrid quantum mechanical–molecular mechanics methods or Poisson–Boltzmann methods.¹⁴

In the next section, the method is described, followed by a description of results on three different types of systems. The first group consists of small clusters of largely saturated molecules. The second group consists of hybrid quantum–classical complexes containing DNA bases. Here, the polarization effects are not entirely due to induction, as defined by eq. (1). The third situation is an investigation of polarization as a flexible molecule (propanol) is rotated and here induction is only a minor contribution to the polarization of the wave function. The suitability of the new method in all three situations is discussed.

Methods

Within classical force fields, polarization is usually described by a set of induced dipoles, μ_i . If we assume that the atomic polarizability, α_i , is isotropic, the μ_i are given by:

$$\mu_i = \alpha_i E_i \quad (1)$$

where E_i is the field at atomic center i due to the permanent charges, q_i^0 , and the induced dipoles,

μ_i . Consequently, μ_i values are usually evaluated to consistency by an iterative process. The atomic polarizabilities were evaluated using the method of Miller and Savchik¹⁵; the values used are given as supporting information.

Elsewhere we have shown that a distributed multipole analysis,¹⁰ involving charges, dipoles, quadrupoles, etc. can be described by a more compact description involving effective multipoles.¹³ The rank of the effective multipoles can be chosen to match the accuracy required, but, generally, charges can reproduce the distributed multipole analysis up to rank one (i.e., charges plus dipoles) whereas charges plus dipoles can reproduce a distributed multipole analysis up to quadrupoles and possibly even octopoles. (This is possible because charges and dipoles distributed over a number of sites contain sufficient parameters to reproduce a multipoles series on one site.) Here, the aim is to reproduce the induced dipoles by effective charges, as illustrated in Figure 1. The potential in the spherical region between r_{low} and r_{up} due to the induced dipole, μ_A , on atom A is reproduced by charges, q' , on atom A and the nearest atoms B, C, and D. The fitting involves integration^{1,11,12} over the region from r_{low} and r_{up} and thus the charges are only strictly valid for interactions in this region. In common with other potential-derived

charge fitting procedures,¹⁶ the charges, q , are obtained by solving the matrix equation:

$$Aq = b \quad (2)$$

where the matrix b contains information on the induced dipoles and the matrix A contains only geometric information.¹¹ Consequently, for each atom in Figure 1, matrix A can be approximated by using a standard geometry. In some applications of this method, this may offer considerable time-saving advantages as A may be precomputed. However, this option was not used here. The final induced charges are obtained by summing over all contributing sites.

The geometries of the complexes in Figures 2, 3, and 4 were optimized using the Hartree-Fock (HF) method¹⁷ (as implemented in the CADPAC 5.0 program¹⁸) with a 6-31G* basis set¹⁹ of approximately double zeta plus polarization quality. The formaldehyde-water heterodimer was optimized with C_s symmetry to prevent the water oxygen from interacting with a formaldehyde hydrogen. The two alternative water trimer structures were generated by superimposing the optimized water dimer onto itself. The DNA geometries were taken from an optimization that used the PM3 semiempirical molecular orbital method.²⁰ The small molecule monomer and complex HF/6-31G* charges were evaluated by our multipole fitting procedure^{1,11,12} from the distributed multipole analysis,¹⁰ which is implemented in CADPAC. The

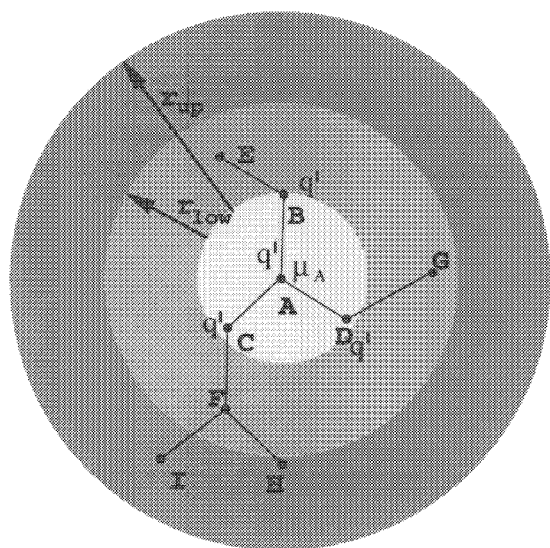


FIGURE 1. A schematic diagram showing how the induced dipole on atom A is converted to induced charges on atoms B, C, and D. The induced dipole on atom A does not contribute to the induced charges on the other atoms (E, F, G, H, and I). The total induced charge is found by summing contributions from induced dipoles on all atoms.

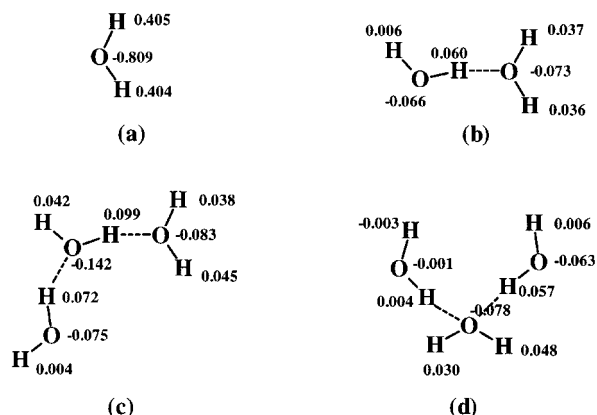


FIGURE 2. Monomer and induced charges for the water system. (a) HF/6-31G* monomer charges. (b) Water dimer showing the induced charges. (c) Cooperative water trimer showing the induced charges. (d) Anticooperative water trimer showing the induced charges. The total charges may be obtained by adding the induced charges to the monomer charges.

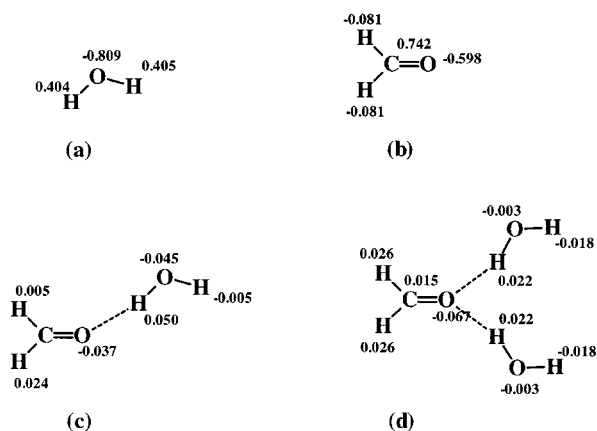


FIGURE 3. Monomer and induced charges for the formaldehyde–water system. (a) HF/6-31G* water monomer charges. (b) HF/6-31G* formaldehyde monomer charges. (c) Water–formaldehyde heterodimer showing the induced charges. (d) Anticooperative formaldehyde–water heterotrimer showing the induced charges.

DNA complex and monomer HF/6-311G* charges²¹ were derived in a similar fashion. (These DMA-based charges are similar but not identical to potential derived charges, as shown in ref. 1.) The self-consistent induced dipoles were evaluated at each atom using an in-house-modified version of AMBER 4.0.²² Intramolecular contributions to the classical field, E_i were restricted to 1–4 and longer range interactions. The induced dipoles were then converted to atomic charge increments (induced charges) using the procedure just outlined. For the DNA systems, these charges were then corrected so that the updated charges for the isolated monomer were identical to the Hartree–Fock monomer charges (*vide infra*). For the methanol systems, the correction was very small and was thus ignored. For the remaining systems there were no 1–4 contributions to the field.

The ability of the new method to evaluate induced charges was assessed by analyzing whether

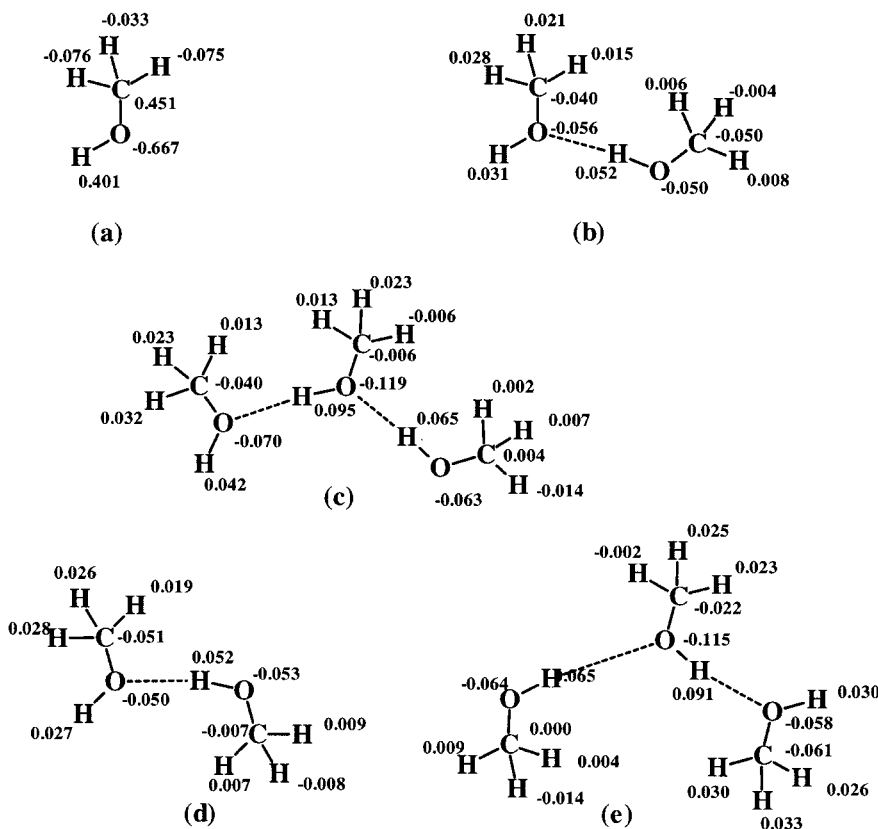


FIGURE 4. Monomer and induced charges for the methanol system. (a) HF/6-31G* methanol monomer charges. (b) Cis dimer showing the induced charges. (c) Cis trimer showing the induced charges. (d) Trans dimer showing the induced charges. (e) Trans trimer showing the induced charges.

the induced charges were in agreement with chemical intuition. The new method was also assessed by regression analysis between the *ab initio* charges for the complex and either the *ab initio* monomer charges or the monomer charges plus the induced charges. The DNA base pair *ab initio* calculations were hybrid quantum mechanical–classical calculations. The hybrid approach has the advantage that basis set superposition effects²³ are minimal.²⁴ This is because the perturbing base had no basis functions, but rather was treated by classical charges. In calculating the updated charges, only the quantum mechanically treated base was allowed to polarize, because the atomic polarizabilities of the classical partner were set to zero. Consequently, there is less ambiguity in the calculations as the polarization of one base is not dependent on the polarization of the other.

For the propanol calculations, the initial charges were taken from the anti–anti (extended) conformation. The other main conformational minima (the anti–gauche, gauche–anti, gauche–gauche [tight] and gauche–gauche [loose]) were optimized and the charges were updated and corrected as above for each of these minima.

Results

Figures 2–4 show the initial monomer charges and the induced charges in the complex resulting from the polarization process—for water,

formaldehyde–water, and methanol. The regression analysis between the updated charges and the corresponding *ab initio* charges is shown in Table I. The full charges for the formaldehyde–water heterotrimer and the anticooperative water trimer are shown in Figure 5. Only selected results for the DNA bases are shown in Figure 6, but the full regression analysis is shown in Table II. The results for propanol are only reported as supporting information because the polarization is not due to induction effects.

Discussion

Two key observations arise from our results. First, our simple induction model reproduces the charge redistribution in the hydrogen bonded complexes both qualitatively and quantitatively. Second, the results show that, when potential derived charges are used in combination with intramolecular induction effects, then a correction to the charges is required to avoid double counting of certain intramolecular interactions. These observations are discussed in more detail in what follows.

COMPLEXES INVOLVING SMALL MOLECULES

Qualitative inspection of the figures shows that the new method produces induced charges in line with chemical intuition. For example, in the water dimer (Fig. 2b), the central hydrogen shows the

TABLE I. Regression Analysis Results for Water, Formaldehyde, and Methanol Systems.^a

Complex	Figure no.	(a) Monomer charges		(b) Updated charges	
		Gradient (<i>m</i>)	Correlation coeff. (<i>r</i>)	Gradient (<i>m</i>)	Correlation coeff. (<i>r</i>)
H ₂ O dimer	1b	0.93 ± 0.01	0.999	1.006 ± 0.004	1.000
H ₂ O trimer ^b	1c	0.90 ± 0.02	0.998	1.010 ± 0.002	1.000
H ₂ O trimer ^c	1d	0.95 ± 0.01	0.998	1.002 ± 0.002	1.000
H ₂ CO — H ₂ O	2c	0.95 ± 0.01	0.999	0.995 ± 0.007	1.000
H ₂ CO — (H ₂ O) ₂ ^b	2d	0.96 ± 0.02	0.997	0.99 ± 0.01	0.999
Cis-MeOH dimer	3b	0.94 ± 0.02	0.997	0.98 ± 0.01	0.998
Cis-MeOH trimer ^b	3c	0.90 ± 0.01	0.996	0.991 ± 0.009	0.999
Trans-MeOH dimer	3d	0.93 ± 0.02	0.995	0.98 ± 0.01	0.998
Trans-MeOH trimer ^b	3e	0.91 ± 0.02	0.995	0.984 ± 0.008	0.999

^aRegression analysis ($y = mx$): column (a), between the HF / 6-31G* monomer charges (y) and the HF / 6-31G* complex charges (x); and column (b), between the updated charges (monomer plus induced charges) (y) and the HF / 6-31G* complex charges (x). The correlation coefficient is denoted r .
^bCooperative arrangement.
^cAnticooperative arrangement.

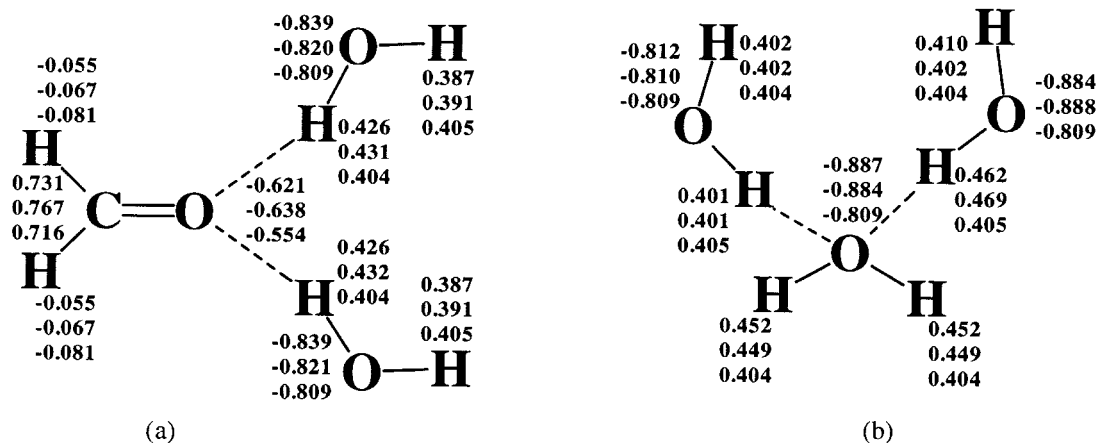


FIGURE 5. Monomer, Hartree-Fock, and induced charges for (a) the formaldehyde-water heterotrimer (see Fig. 3d) and (b) the anticooperative water trimer (see Fig. 2d). The charges are reproduced in the order-induced charge (top), Hartree-Fock charge (middle), and monomer charge (bottom).

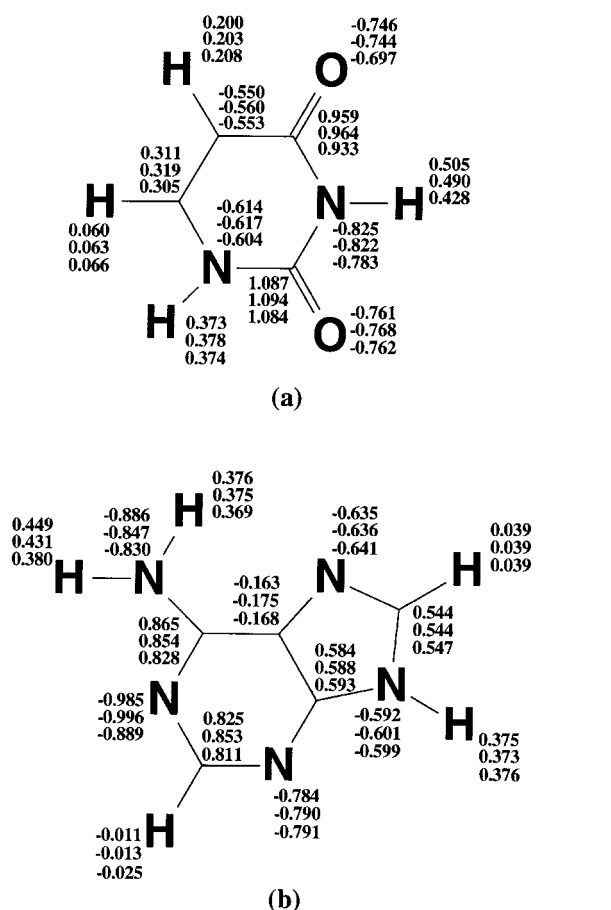


FIGURE 6. Monomer, Hartree-Fock, and induced charges for (a) uracil and (b) adenine perturbed by adenine and uracil, respectively. The charges are reproduced in the order-induced charge (top), Hartree-Fock charge (middle), and monomer charge (bottom). The results for adenine and thymine are similar.

largest induced charge, whereas the hydrogen furthest from the hydrogen bond shows the smallest induced charge. The water trimer in Figure 2c is cooperative,²⁶ which means that the two hydrogen bonds should reinforce each other to generate a more polar system, whereas in Figure 2d the water trimer is anticooperative²⁶ and so there should not be such a large increase in polarity. Indeed, the bridging hydrogens in Figure 2c carry larger induced charges than in Figure 2b, whereas in Figure 2d they carry smaller induced charges. Likewise, the central oxygen in Figure 2c carries a much larger induced charge than in Figure 2d. There is an asymmetry in Figure 2d because the symmetry was not rigorously imposed; the *ab initio* charges show a similar asymmetry (see Fig. 5). Given that the geometry and initial charges show approximate symmetry, this is a strong indication of the ability of the classical induction method to reproduce *ab initio* charges with significantly less computational effort.

The formaldehyde-water heterotrimer in Figure 3d is anticooperative and, although there is a larger induced charge on the carbonyl oxygen, the water-induced charges in Figure 3d are lower than those in Figure 3c. The induced OH charges in the formaldehyde-water heterodimer are comparable to those in Figures 2b and 4b. The results for the two methanol dimers (Fig. 4b and d) are comparable as are those for the two trimers (Fig. 4c and e). The heterotrimers in Figure 4c and e are both cooperative and clearly show induced charges, which are significantly enhanced over those for the dimers (Fig. 4b and d).

TABLE II.
Regression Analysis Results for the DNA Systems.^a

Complex $\Psi:q$	Figure no.	(a) Monomer charges		(b) Updated charges		(c) Corrected, updated charges	
		Gradient (m)	Correlation coeff. (r)	Gradient (m)	Correlation coeff. (r)	Gradient (m)	Correlation coeff. (r)
U:W _b	6a	0.984 ± 0.007	0.999	0.997 ± 0.040	0.980	1.000 ± 0.002	1.000
U:A		0.969 ± 0.009	0.999	0.993 ± 0.040	0.996	0.996 ± 0.003	1.000
U:W _t		0.999 ± 0.006	1.000	1.010 ± 0.040	0.982	1.012 ± 0.004	1.000
U:W _{t,b}		0.938 ± 0.008	0.999	1.010 ± 0.040	0.981	1.010 ± 0.004	1.000
A:U	6b	0.960 ± 0.010	0.998	0.932 ± 0.007	0.980	0.995 ± 0.007	0.999
A:T		0.960 ± 0.010	0.998	0.928 ± 0.040	0.980	0.997 ± 0.007	0.999
T:W _b		0.967 ± 0.008	0.999	0.971 ± 0.030	0.984	0.995 ± 0.003	1.000
T:A		0.988 ± 0.007	0.999	0.978 ± 0.040	0.973	0.998 ± 0.002	1.000
T:W _t		0.997 ± 0.005	1.000	0.984 ± 0.040	0.974	1.005 ± 0.006	1.000
T:W _{t,b}		0.985 ± 0.006	0.999	0.985 ± 0.040	0.974	1.005 ± 0.004	1.000

^aRegression analysis ($y = mx$): column (a), between the HF/6-311G* monomer charges (y) and the HF/6-311G* complex charges (x); column (b), between the updated charges (monomer plus induced charges) (y) and the HF/6-311G* complex charges (x); and column (c), between the updated and corrected charges (y) and the HF/6-311G* complex charges (x). The correlation coefficient is denoted r . (The correction ensures a perfect correlation for the isolated monomers.) A denotes adenine, T denotes thymine, U denotes uracil, and W denotes water. The subscript t (W_t) denotes a water molecule hydrogen bonding to the top oxygen of U (or T) (O⁴) in Figure 6; the subscript b (W_b) denotes a water molecule hydrogen bonding to the bottom oxygen of U (or T) (O²) in Figure 6; W_{t,b} denotes two water molecules hydrogen bonding to both carbonyl oxygens of U (or T) in Figure 6. The quantum partner is denoted Ψ ; the classical partner is denoted q .

Figure 5 shows the classically derived charges and Hartree–Fock-derived charges for two of the test systems. Qualitatively, we see that the classically derived charges are comparable to those of the HF charges. For the formaldehyde system (Fig. 5a), the classical induction is in the right direction and comparable to the HF calculations. For the water trimer (Fig. 5b) the classically updated charges are almost identical to the HF charges; as noted earlier, this is particularly remarkable given the asymmetry exhibited by the system.

The comparisons in Table I show that not only is there good qualitative agreement, but that in the majority of cases there is also excellent quantitative agreement. Perfect agreement would demand a gradient of 1.0 between the updated charges (y), evaluated using the induced charges, and the HF/6-31G* complex charges (x). Previous work¹ suggests a gradient of about 0.9 between the HF/6-31G* monomer charges (y) and the HF/6-31G* complex charges (x), and so we are certainly looking for a gradient nearer to 1.0 than 0.9. In all cases, this latter criterion has been met and in four of the nine cases the stricter criterion of a gradient equal to 1.0 has been met when the error in the gradient has been taken into account. For each set of updated charges, the error in the gradient is no more than approximately 0.01, whereas, for the monomer charges, the gradient is on average in error by 0.07. Likewise, the correlation coefficient

(r) is also higher for the updated charges. These results are clearly very encouraging, particularly as no attempt has been made to optimize the atomic polarizabilities. The excellent agreement here is probably because the polarization effects are almost entirely due to induction.

DNA

For DNA systems, it is important to note that the monomer charges show a reasonably high correlation with the Hartree–Fock complex charges. This is because the bases are bigger and so generally a smaller fraction of the molecule is heavily perturbed. This is illustrated by comparing the gradient for adenine (15 atoms, 2 rings) perturbed by uridine (0.969 in Table II, column a, “Monomer charges”) with that for uridine (12 atoms, 1 ring) perturbed by adenine (0.960). With this in mind, we note that the initial DNA results were not good (see Table II, column b, “Updated charges”) as the updated charges for the complexes had less correlation with the *ab initio* charges than the original monomer charges. This led to the realization that the monomer charges had to be corrected for intramolecular induction effects. The argument for a correction is as follows. In many force fields, the atomic charges are derived to reproduce a quantum mechanical (reference) electrostatic potential and, as such, are the optimum charges to describe

the electrostatic interactions of a molecule at a given level of theory and basis set. If a classical induction model is now added to the force field, the optimum atomic charges, although they already implicitly include intramolecular induction effects, will be supplemented with induced charges or induced dipoles and will therefore no longer be optimum. In our implementation of polarization based on the AMBER force field, this effect will occur for any molecule with a 1–4 nonbonded interaction. This effect underlies the poor initial results reported in column b of Table II.

There are two potential solutions to this problem. The simplest is to ignore all intramolecular induction effects, but this would ignore internal induction arising as a secondary effect of intermolecular induction. Further, it is clearly wrong to ignore intramolecular effects for large molecules such as proteins, especially as charges are usually determined for fragments of large molecules and thus interactions between these fragments would be missing. Here, we propose that the initial point charges plus the internal induction effects (represented by induced dipoles or induced charges) should reproduce the reference molecular electrostatic potential. Because our DNA calculations involved only one polarizable molecule per test system we applied the correction by subtracting the induced charges derived from isolated gas phase calculations and this was done after all the calculations were completed. In practice, where many molecules in a system may be polarizable, the correction should be made during the charge fitting procedure. This could be achieved by modifying the value of the initial charges through subtraction of the incremental charges until consistency with the reference molecular electrostatic potential has been achieved. The corrected updated charges are given in column c of Table II, and these are the results that will be discussed in more detail in the rest of this section.

The results in Table II show the same excellent quantitative agreement between the *ab initio* complex charges and the updated (and corrected) charges. Nevertheless, analysis of the gradients in Table II shows an improvement in the description of nine of the ten DNA systems (all except U:W_i—compare columns a and c), and analysis of the correlation coefficient shows an improvement in all ten systems. In eight of the ten systems, the gradient plus the error differs from unity by only 0.002 or less and in the remaining two systems the discrepancy is no more than 0.008. Inspection of Figure 6a shows that both the updated and

Hartree–Fock charges change as expected. For example, the C4—O⁴ carbonyl group (top) becomes more polar as more electron density is drawn toward the oxygen by the positive charges representing the —NH₂ group of adenine, but the C2—O² carbonyl group (bottom of Fig. 6a) hardly changes, because it is not involved in hydrogen bonding. A similar effect is seen on the N3—H group (right) as electron density is attracted by the negative charge representing N1 of adenine. Figure 6b also shows the expected change in polarity. The adenine H—N⁶ bond involved in hydrogen bonding becomes more polar, and the N1 atom becomes more negative (both on left-hand side of Fig. 6b). This agreement for DNA is remarkable, particularly because the polarization may not be a pure induction effect, but rather may become more delocalized through conjugation effects involving the π system. Figure 5 shows similar results for the formaldehyde–water heterotrimer (see also Fig. 3d) and the anticooperative water trimer (see Fig. 2d); again, comparison between the *ab initio* charges and the updated charges is very good.

CONFORMATIONAL EFFECTS IN PROPANOL

Although propanol has limited conformational flexibility, large errors in the dipole moment and free energy of hydration can result if the same set of charges is used for each conformation.¹⁶ Our calculations over the various minima show that the induced charges may be much smaller than the changes predicted by the Hartree–Fock method (0.005 vs. 0.05 average magnitude for the OH group) or much larger (0.12 vs. 0.002 for the terminal carbon). Here, we believe the polarization is not due to induction alone but is more aptly described as a change in the molecular orbital vectors as the orbitals rotate with conformation. Thus, our calculations show that induced charges are not suitable for treating this electronic effect. This problem has been discussed elsewhere²⁵ and alternative strategies for modeling the changes in atomic charges with conformation are required.^{16, 25}

Conclusions

We have presented a method of updating atomic charges from induced dipoles in classical mechanics calculations. The method is based on our approach of evaluating charges (and effective multipoles) from a distributed multipole analysis.^{1, 11, 12} The induced charges convey more chemical mean-

ing than induced dipoles as they are easier to interpret in terms of charge rearrangement. In particular, the method predicts induced charges in line with experimental information²⁶ on hydrogen bonding effects in cooperative and anticooperative systems such as the water trimer, the methanol trimer, and the formaldehyde–water heterotrimer. Excellent quantitative agreement has been obtained between the updated charges and the corresponding charges evaluated using *ab initio* methods for the water, formaldehyde–water and methanol complexes, and various complexes involving nucleic acid bases. This method may therefore have applications in a number of different situations in which polarization effects are important such as molecular mechanics, molecular dynamics, Monte Carlo methods, and possibly even Poisson–Boltzmann methods and hybrid quantum mechanics—molecular mechanics methods. The main advantage of this method is that induced charges are easier to interpret and manipulate than induced dipoles.

Possibly the most important point to arise from this work is the need to apply a correction to the underlying atom-centered point charges when a classical induction model is used to augment the electrostatic description. For molecules with 1–4 and higher nonbonded interactions that contribute to the induction effects (e.g., in the AMBER force-field), this correction is essential.

The approach outlined here will have distinct advantages in certain situations; however, the use of atomic charges instead of higher rank multipoles may result in significant errors in other situations. In such situations there may be advantages in treating both electrostatics and induction at the dipole level, as discussed in ref. 13. Most importantly, the effective dipole approach and the multipole-derived atomic charge method outlined here could be combined, because the underlying methodology based on Figure 1 to derive the induced charges is essentially the same as that used to derive the effective multipoles.¹³

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Supplementary Material

Polarizabilities, atomic coordinates, *ab initio* charges, updated charges, and where appropriate updated and corrected charges of the complexes (4 pages) can be obtained.

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